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Pathogenesis and Treatment Perspectives of Chronic Graft Rejection (CVR)

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INTRODUCTION

Chronic rejection is one of the major threats to graft function on a long-term basis in heart and kidney transplantation. During the last decades the results of organ transplantation have improved steadily, whereas the annual rate of graft loss after the 1st post-transplantation year has not changed significantly (Cook & Terasaki 1989, Thorogood et al. 1992). The diagnosis of chronic rejection is based on a combination of clinical, morphological and angiographic findings. The histopathology of chronic renal transplant rejection is characterized by various degrees of narrowing of the graft arteries and arterioles, interstitial cellular infiltration and fibrosis, tubular atrophy and variable glomerular changes (Maryniak et al. 1985, Kasiske et al. 1991, Paul & Fellström 1992). The vascular narrowing results from infiltration of the intima by mononuclear cells, migration and proliferation of vascular smooth muscle cells and fibroblasts from the media into the intima and subsequent deposition of extracellular matrix material. The histopathological picture of chronic heart graft rejection is characterized by atherosclerotic vascular changes in combination with variable degrees of interstitial fibrosis (Gao et al. 1987, Cary 1992). The atherosclerotic vessel wall lesions are important features of chronic rejection in hearts and kidneys, but are not specific since they may also be observed in other vascularized organ allografts.

It has been estimated that renal graft failure due to chronic rejection is the leading cause of 6-12% of graft losses observed after the initial 5-10 years following transplantation (Mahony & Sheil 1987, Paul & Fellström 1992). It was also estimated that 25% of the cumulated graft losses in the first 3 posttransplant years were due to chronic rejection in the early 1980s. Systematic annual coronary

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angiography studies of cardiac allografts suggest that 40–60% of grafts have significant vascular changes within 5 years following transplantation that are indicative of chronic rejection.

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The pathophysiology of chronic rejection is complex and it is difficult to pin-point a single leading cause. Notwithstanding morphologic and functional similarities between the vessel wall lesions of graft atherosclerosis and "naturally occurring" atherosclerosis, it may be assumed that the former is a manifestation of atherosclerosis partially driven by allogeneic immune mechanisms. The pathogenesis involves a number of mechanisms which have been demonstrated to be involved in the progression of the arteriopathy (Fig. 1). Even though the endothelium may remain intact in a vessel undergoing atherosclerotic transformation, early endothelial cell damage is often present and may be due to a number of causes. In transplantation such possible causes are ischemic and reperfusion damage (Ross 1986, Lehr et al. 1992). In an experimental model of transplant atherosclerosis in aortic grafts in the rat we could show that the cold ischemia time is important for the development of intimal hyperplasia in the graft (Wanders et al. 1993). The presence of the endothelial cell antibodies (Dunn et al. 1992) followed by complement activation or release of specific enzymes such as heparinases (Naparstek et al. 1984) may also damage the endothelium. The deposition of LDL cholesterol or oxidatively modified lipoproteins may cause structural or functional endothelial damage (Ross 1986, Steinberg 1989). An endothelial cell dysfunction has also been demonstrated in hypercholesterolemia, hypertension and in atherosclerosis, leading to a reduced synthesis of endothelial-derived relaxing factor (EDRF = nitrous oxide, N.O.). A similar type of endothelial cell injury with a reduced EDRF could also be demonstrated following exposure to oxygen radicals at reperfusion (Lüscher 1990a, b). Furthermore, presence of reactive oxygen radicals may form highly cytotoxic peroxynitrates together with N.O., which could cause further damage to the tissue (Froeman 1993).

The initial endothelial cell damage may be followed by monocyte or macrophage influx into the subendothelial compartment and also a deposition of platelet granule proteins. The endothelial cell will react to the damage and to the release of cytokines including interferon- γ , interleukin-1 and TNF- α by an increased expression of adhesion molecules (Patarroyo et al. 1990, Springer 1990, Hansson et al. 1993, Taylor et al. 1992), upregulation of class-II antigen expression and increased permeability to plasma proteins. In particular, the adhesion structures ICAM-1, VCAM-1 and ELAM-1 may become upregulated through the influence of cytokines. The dynamics in the expression of these adhesion structures are different, however. As mentioned below, the presence of oxidized LDL also has the potential of influencing the expression of adhesion structures (Froestegård

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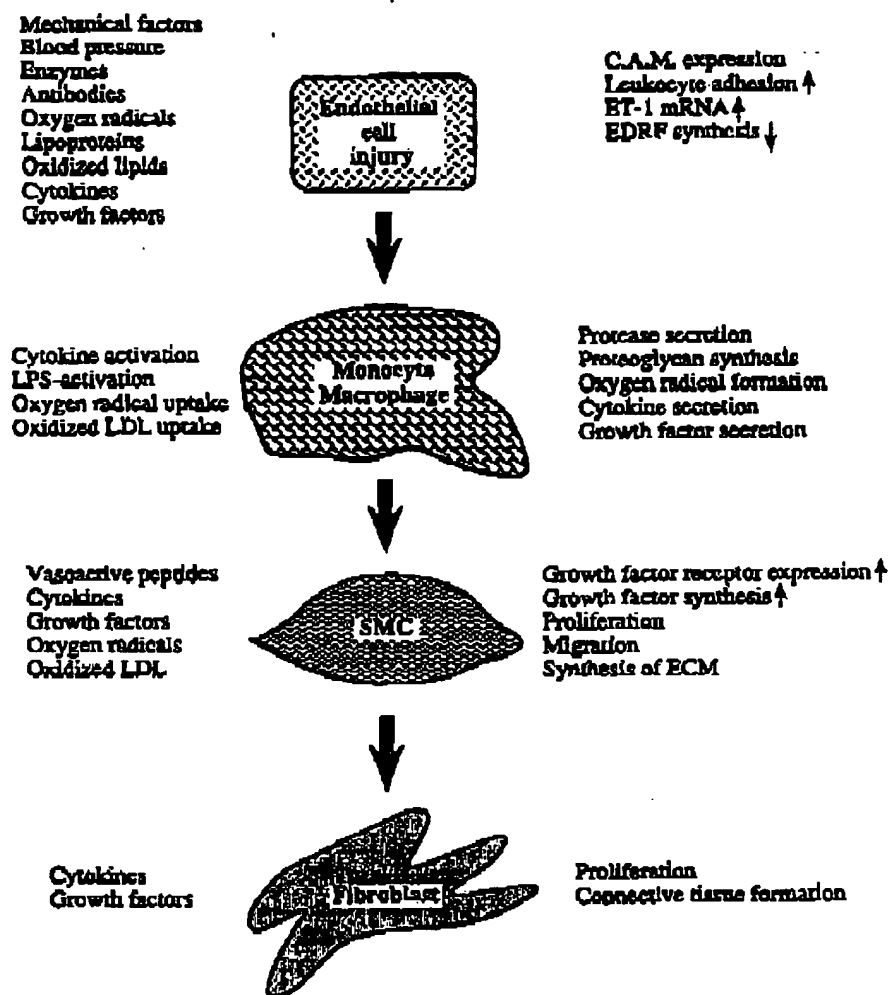


Figure 1. Pathogenic network in the development and progression of transplant atherosclerosis in chronic graft rejection. SMC = smooth muscle cell; ET = endothelin; EDRF = endothelial-derived relaxing factor; ECM = extracellular matrix.

1994). Counteracting effects of N.O. on ICAM-1 expression may appear secondarily. The activation of endothelial cells, smooth muscle cells and infiltrating monocytes or macrophages participating in the vessel wall injury may produce multifunctional cytokines and growth factors which may induce cell proliferation

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and migration of smooth muscle cells (SMC) through paracrine, autocrine or juxtacrine pathways. The growth and migration of SMC is an important event in the development of intimal hyperplasia and early atherosclerosis in the vessel wall in the graft. Growth stimulation of SMC may be induced directly by PDGF, endothelin-1 and thrombin or indirectly through the action of interleukin-1 (IL-1), TNF- α , TGF- β , vasoconstrictive substances (endothelin-1, angiotensin-II, thromboxane-A₂) or oxidized LDL cholesterol. The most important chemoattractants of SMC are PDGF, TGF- β , IL-1 and IGF-1, which may be operative in the migration of SMC from the media into the proliferating intima. The appearance of smooth muscle cells in proliferating intima could be clearly demonstrated in our own experimental grafts such as the aorta through stainings with α -actine antibodies (Wanders et al. 1993). In allogeneic grafts we also found that a substantial depletion of the media volume took place, which may be counteracted by pharmaceutical interventions which effectively attenuated the process (Åkdyrek et al. 1993).

The list of cytokines and growth factors possibly involved in tissue remodelling of chronic graft rejection is long. There is evidence that platelet-derived growth factor (PDGF) plays an important role in the development of chronic rejection, similar to normally occurring atherosclerosis. PDGF may be released and deposited when platelets aggregate or become activated in the vascular wall and it may also be secreted by a number of cells including monocytes and macrophages (Shimokado et al. 1985), endothelial cells (DiCorleto & Bowen-Pope 1983), vascular smooth muscle cells (Nilsson et al. 1985) and glomerular mesangial cells (Silver et al. 1989). PDGF has also been demonstrated to be present in renal transplants undergoing chronic rejection as well as in experimental heart transplants in the rat simulating chronic rejection. The expression and secretion or increased transcript of PDGF has been shown to be regulated by certain cytokines, vasoactive peptides (angiotensin-II) or oxidized LDL cholesterol. One of the intriguing connections between hypertension and atherosclerosis is the fact that several vasoconstricting substances such as angiotensin-II, endothelin-1 and thromboxane-A₂ may exert a direct growth stimulation of smooth muscle cells or induce proliferation synergistically with growth factors such as PDGF-AA, or b-FGF. This may explain SMC hypertrophy or proliferation induced by vasoactive peptide.

Two types of PDGF receptors exist on the plasma membrane in a number of mesenchymal cells: α - and β -receptors (Heldin et al. 1988). α - and β -receptors are both found in varying density on fibroblasts and SMC, whereas mesangial cells express mainly β -receptors (Wallmon et al. 1993). Apart from growth stimulation by the ligand, fibroblasts have also been shown to increase the synthesis of extracellular matrix substance when exposed to PDGF, in particular hyaluronic acid (HA). Increased amounts of HA could be demonstrated in our chronically rejected renal grafts (Wells et al. 1990, 1993) and in experimental aorta grafts

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(Stauffer et al. 1993). PDGF-AA binds only to the α -receptor whereas PDGF-BB may bind either to β - or α -receptors with different affinities. The expression of PDGF receptors may be modified or regulated by TGF- β or by oxidized LDL-cholesterol (Stiko-Rahm 1992). It has been demonstrated that PDGF β -receptors may be upregulated in tissues going through a chronic inflammatory process, including rheumatoid arthritis (Rubin et al. 1988) and kidneys with chronic vascular rejection (Fellström et al. 1989) as well as experimental glomerulosclerosis (Floege et al. 1992). We found similarly increased receptor expression of PDGF α -receptors on smooth muscle cells in experimental heart and aorta transplants in the rat (Waltenberger et al., unpublished observations).

Graft arteriosclerosis is usually more diffuse and widespread than a normally occurring atherosclerosis, possibly because it is initiated and possibly propelled by the allogeneic immune reaction in the graft vessel wall. Subsequent vasculitis and activation of vascular wall cells may result in local production of growth-promoting substances along with substances secreted by infiltrating inflammatory cells such as γ -interferon, IL-1, TNF- α , and TGF- β produced by T cells. TGF- β may be of particular interest since it may modulate the immune or the inflammatory reaction due to its potential to either stimulate or inhibit growth and differentiation of immune cells, mesenchymal cells and SMC. TGF- β may also stimulate the synthesis of extracellular matrix proteins and production of connective tissues from fibroblasts (Ruscetti & Palladino 1991). Using monoclonal antibodies recognizing TGF- β 1 and the latent TGF-binding protein (LTBP), we could demonstrate that TGF- β 1 is present in experimental transplant atherosclerosis in both hearts and vessels (Waltenberger et al. 1992a, b). Through extraction of mRNA from these tissues followed by northern blot analysis we could also demonstrate that it was mainly TGF- β 1 and that TGF- β 1 activity was present in protein extracted from these tissues (Waltenberger et al. 1993b).

Hyperlipoproteinemia has an established role in the development of naturally occurring atherosclerosis (Ross 1986, Steinberg 1989, Ragnström et al. 1992). In particular there is a correlation between hypercholesterolemia and the incidence of atherosclerotic lesions. In the renal transplant patients with chronic vascular rejection whom we investigated, it was demonstrated that they had increased lipoprotein levels compared with patients with a stable graft function (Dimény et al. 1993a). In particular, it was found that patients with chronic rejection had an atherogenic pattern of lipoproteins and that there was a correlation between the degree of hyperlipidemia and the extent of pathological changes indicative of chronic rejection in graft biopsies (Dimény et al. 1993b). In a prospective study in 133 renal transplant patients we also found that there was a distinct relation between graft function at 6 months post-transplantation and the degree of hyperlipoproteinemia at a time point preceding transplantation (Dimény et al. 1993c). The reason for this relationship may be linked to an assumed propensity for oxidation of LDL cholesterol in a graft with an ongoing inflammatory process

and the ability of oxidized LDL to induce class-II antigen expression (Frostedgård et al, 1990). Since there is also a connection between the frequency of acute rejections and the development of chronic graft rejection, this may be another mechanism by which hyperlipoproteinemia increases the risk for development of CVR. Furthermore, the development of intimal hyperplasia in transplanted hearts in the rat was accelerated when the animals were fed a cholesterol-enriched diet (Fellström et al. 1990). Since the uptake of lipoproteins in the vascular wall is associated with an influx of monocytes, which may ingest LDL particles and become activated, a subsequent release of growth substances such as PDGF-B-like peptides is a possible link between lipoproteins and the induction of cell proliferation in the vascular wall (Ross 1986).

In the vascular wall of grafts going through chronic vascular rejection there is almost constantly a more or less pronounced infiltration of T lymphocytes and macrophages (Fellström et al. 1988). The macrophage, which is frequently present in the tissue in chronic graft rejection, has the potential of synthesizing and secreting a number of cytokines and growth factors which may be of importance for the development of vascular remodelling and fibrosis (Fig. 2). Such growth factors include PDGF, b-FGF and heparin-binding-EGF, but

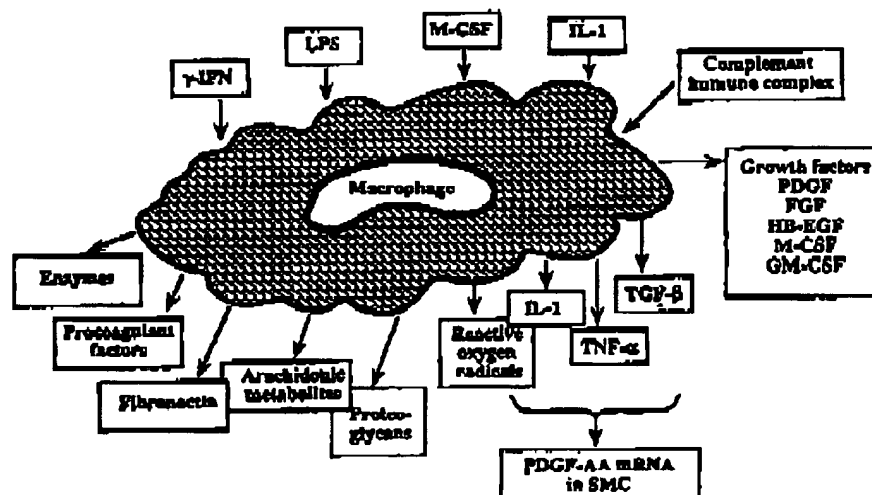


Figure 2. Characteristics of the monocyte/macrophage which may be important for the development of chronic graft rejection or transplant atherosclerosis. IFN = interferon; LPS = lipopolysaccharide or endotoxin; M-CSF = monocyte colony-stimulating factor; IL-1 = interleukin-1; TGF- β = transforming growth factor- β ; TNF- α = tumor-necrosis factor- α ; PDGF = platelet-derived growth factor; FGF = fibroblast growth factor; HB-EGF = heparin-binding epidermal growth factor.

IL-1, TGF- β and TNF- α may also increase the transcript of PDGF-AA in SMC. Another important factor is the induction of oxygen radical damage to the vascular wall and the interstitial tissue, which may take place by a direct effect of reactive oxygen species, through the formation of oxidatively modified LDL-cholesterol or through the formation of highly cytotoxic peroxynitrates. Thus, it may be assumed that the *oxidative modification of LDL cholesterol* is enhanced in cases with chronic vascular rejection. Based on the studies by a group at the Department of Medicine, Karolinska Institute, oxidatively modified LDL may be an important inducer of changes in the vascular wall accelerating the atherosclerotic process. It was demonstrated that oxidized LDL causes a release of a mononuclear leukocyte factor which stimulates the expression of ICAM-1, VCAM-1 and ELAM-1 leading to an increased adhesion of monocytes to endothelial cells (Frostedg rd et al. 1991). Furthermore, oxidized LDL may also increase class-II antigen expression on human monocytes (Frostedg rd et al. 1990), and increase the expression of PDGF-A chain transcripts in smooth muscle cells and the expression of both α - and β -receptors of PDGF on smooth muscle cells, as well as a subsequent enhanced responsiveness of SMC to exogenous PDGF (Stiko-Rahm et al. 1992, Nilsson 1993) (see Fig. 3). As mentioned above, the synthesis of EDRF in endothelial cells may become impaired by oxidized LDL. Thus, it seems as if the oxidation process in the vascular wall and the oxidative modification of LDL cholesterol may play an important role in the early development of intimal hyperplasia and atherosclerosis seen initially in the development of chronic vascular rejection. This is the background for trials with antioxidant agents such as Probucol[®] in chronic graft rejection and other trials which will be initiated.

Prostaglandins, prostacyclins and thromboxane have been recognized to be important mediators of various biological processes and have also been shown to be disturbed in chronic rejection. An imbalance has been demonstrated with high thromboxane levels and normal or slightly decreased prostacyclin levels. Since thromboxane may enhance the immune reactivity, stimulate platelet aggregation, cause vasoconstriction and smooth muscle cell proliferation, the increased levels of thromboxane have been postulated to be of pathogenetic importance for the development of chronic rejection. Prostacyclin, on the other hand, inhibits platelet aggregation and smooth muscle cell proliferation and also causes vasodilatation (Sinzinger et al. 1987, Teraoka et al. 1987b).

The described factors are believed to be of importance for the development of chronic vascular rejection of transplanted organs. They are the basis for the strategies used in the treatment or prevention of chronic rejection. The pathophysiology is rather complex and no single factor could be pointed out to be more important than others. This is basically the reason for various approaches having been made with the aim of abrogating the chronic graft rejection process.

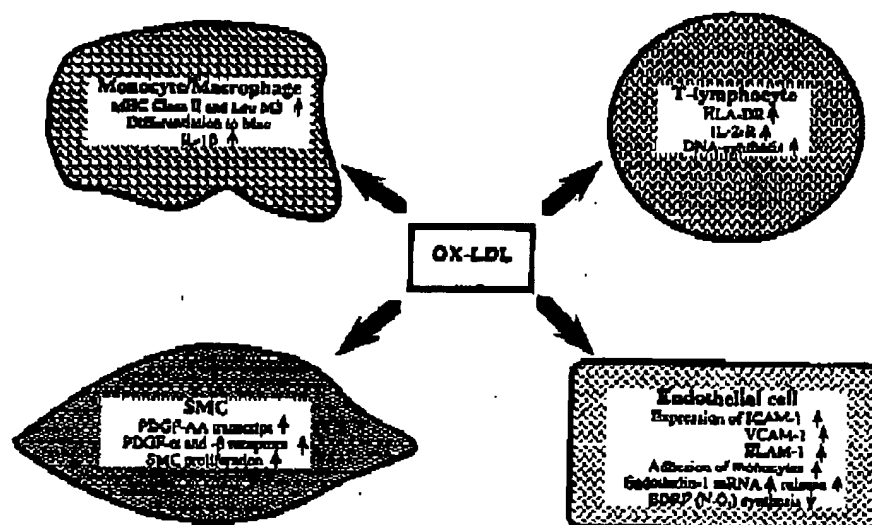


Figure 3. Effects of oxidatively modified LDL on factors promoting (transplant) atherosclerosis or chronic graft rejection (adapted from the work of Frostegård et al.). PDGF = platelet-derived growth factor; SMC = smooth muscle cell; MHC = major histocompatibility complex; IL-1 β = Interleukin-1 β ; EDRF = endothelial-derived relaxing factor; IL-2R = interleukin-2 receptor; ICAM = intercellular adhesion molecule; VCAM = vascular cell adhesion molecule; ELAM = endothelial adhesion molecule.

PREVENTION AND TREATMENT OF CVR

There is a very limited experience to date with therapeutic intervention and most data emerge from experimental studies while clinical studies have been limited and difficult to assess because of lack of accepted criteria to diagnose chronic rejection. Many of the studies are also uncontrolled and difficult to analyze because of concomitant drug therapies. Therapeutic strategies have largely been based on interference with metabolic disturbances considered to be of pathogenic significance.

Infiltrating inflammatory cells may participate in the development of intimal hyperplasia in chronic vascular rejection. Since lymphocytes and monocytes may secrete destructive enzymes, cytokines and growth factors and participate in the formation of reactive oxygen radicals and enhance the *in situ* oxidation of the LDL fraction of lipoproteins and subsequently activate endothelial cells, it is fair to anticipate an important role for these cells in the development of chronic vascular rejection. For this reason it may also be assumed that chronic rejection is partly the result of suboptimal immunosuppression (Kuo & Monaco 1993).

Therefore, the HLA match, the presence of one or more previous episodes of acute rejection, previous rejection of kidney transplants and presence of panel-reactive antibodies may participate in development of chronic graft rejection. Furthermore, the commonly used immunosuppressive agents such as cyclosporine A and prednisolone may also have a pro-atherogenic potential. Cyclosporine A has been shown to have direct toxic effects on vascular endothelial and smooth muscle cells (Zoja et al. 1986, Ferns et al. 1990) and steroids may indirectly have a detrimental effect because of induction of hyperlipidemia and increased peripheral insulin resistance. On the other hand, some of the more recently developed and investigated drugs like Rapamycin and RS-61443 seem to have advantageous effects on chronic rejection, based upon recent experimental results (Morris et al. 1991). Thus, *optimising the immunosuppressive treatment* in organ transplantation may be an important first objective in the prevention of the development of chronic vascular rejection.

Prostaglandin modulators have been frequently tried in the prevention and the treatment of chronic vascular rejection, both clinically and experimentally, aiming at restoration of the thromboxane-prostacyclin imbalance present in renal chronic rejection. Continuous infusion of the synthetic prostacyclin analogue Iloprost® had a beneficial effect on the development of cardiac graft atherosclerosis in a rat model of long-term survival of heart transplants following limited cyclosporine treatment (Fellström et al. 1991). In preliminary reports on the use of prostacyclin analogues in renal transplant patients with an established chronic vascular rejection, beneficial effects were reported (Teraoka et al. 1987b). This study was made in a limited number of patients and with a limited observation period. In our own open, uncontrolled pilot study a continuous intravenous infusion of epoprostenole was administered for 1 week, followed by a low dose of oral salicylate (100-150 mg daily) and dipyridamole (225 mg daily). In 22 patients with an established chronic renal allograft rejection, we saw a stabilization or improvement of function compared with pretreatment levels in 18/22 patients followed at least 12 months (Fellström et al. 1993). These data suggest that treatment with prostacyclin analogues and cyclooxygenase inhibitors may have some therapeutic potential, although controlled studies are still lacking.

Thromboxane antagonists with anti-atherogenic potential due to the properties of thromboxane to stimulate smooth muscle cell proliferation, platelet aggregation and cause vasoconstriction have been tried in renal transplant patients with chronic rejection (Teraoka et al. 1987a). The thromboxane synthetase inhibitor OKY-046 was used and to date 20 patients were treated with OKY-046 and compared with 20 control cases. There was a significantly lower frequency of graft losses in the actively treated patients compared with the control group in a 12-months perspective (Teraoka et al. 1993).

Polysaturated fatty acids of the omega-3 series cause a shift in the thromboxane and prostacyclin metabolites, leading to a decreased platelet stickiness and

aggregability as well as a vasodilatation. Food supplementation with Omega-3 fatty acids causes a slight reduction in hypertriglyceridemia and also reduces the risk of development of atherosclerosis (Weiner et al. 1986, Leaf & Weber 1988). Omega-3 fatty acids may be of particular interest in transplanted patients because they also enhance the immunosuppressive properties of cyclosporine A (Endres et al. 1989). Furthermore, a decrease in the synthesis of PDGF-B-like peptides in endothelial cells may be achieved. Renal transplant patients with a progressive decline in graft function due to chronic rejection were treated with MAXEPA supplementation, which resulted in a significant reduction in the rate of function deterioration compared with pretreatment levels (Sweny et al. 1989, Sweny 1993). The treatment also caused a significant decrease in serum triglycerides and platelet aggregability. The authors are satisfied by the treatment results, and now they administer MAXEPA to all patients with this diagnosis.

The importance of *hyperlipidemia* for development of atherosclerosis is well established (Ross 1986) and evidence has also emerged from our own studies of a possible role of lipoproteins in the development of chronic vascular rejection (Dimény et al. 1993). The use of cholesterol synthetase inhibitors in cardiac transplant patients reduced hypercholesterolemia without lowering HDL cholesterol (Kobashigawa et al. 1990). To date there are no controlled studies showing an effect on the progression of chronic vascular rejection by cholesterol synthetase inhibitors or other lipid-lowering agents. As discussed above, there may be a rationale in using antioxidant agents in transplanted patients with chronic rejection. The antioxidant agent Probucol[®], which has a weak cholesterol-lowering effect (Steinberg 1986) is currently used in a clinical trial in renal transplant patients, but to date no results on the effect on chronic rejection have been reported.

Heparin and *heparin derivatives* inhibit smooth muscle cell proliferation *in vitro* and *in vivo* (Castellor et al. 1982, Clowes & Clowes 1989) independent of their anticoagulant effect. Heparin may also attenuate the migration of smooth muscle cells into the intima and cause a shift in the matrix composition with a decrease in elastin and collagen and an increase in heparan sulphate and chondroitin sulphate (Clowes & Clowes 1989). To what extent these effects are dependent on the potential of heparin to bind the b-FGF, PDGF or macrophage-derived heparin-binding EGF (HB-EGF) is still a hypothetical question. However, a protection of the vascular endothelium by heparin and heparin derivatives seems to be present. The effect upon transplant intimal hyperplasia has been demonstrated experimentally with low molecular weight heparin in combination with cyclosporine (Plissonnier et al. 1992) and according to our own experience there are heparin derivatives without anticoagulant effects, which efficiently protect aorta grafts against development of intimal hyperplasia (Stafberg et al. 1993). To our knowledge there are no clinical studies in transplanted patients with heparin-like substances presented as yet.

The *somatostatin analogue angiopeptin* is a promising substance tested in the prevention and in the treatment of accelerated transplant atherosclerosis. Angiopeptin has all the common endocrine effects of a somatostatin, including reduced levels of growth hormone, insulin and glucagon and is considered to be a non-toxic and non-immunogenic peptide, which can be administered as a continuous intravenous infusion or as intermittent subcutaneous injections. Angiopeptin inhibits cell proliferation in the rabbit aorta after balloon angioplasty (Asotra et al. 1989, Conte et al. 1989). Treatment with angiopeptin also causes a 20-70% inhibition of myointimal proliferation in models of transplant atherosclerosis, including accelerated heart graft atherosclerosis in cholesterol-fed and cyclosporine-treated rabbits (Foegh et al. 1989a, 1989b) and rats (Fellström et al. 1991). In our aorta transplants in the rat, angiopeptin was also shown to inhibit the intimal proliferation by 40% in syngeneic grafts and by 20% in allogeneic grafts, when the recipients were not treated with any immunosuppressive agent (Wanders et al. 1993, Aküyrck et al. 1993). Today, angiopeptin is on clinical trial in heart transplantation and in renal transplantation with the objective of preventing or treating chronic vascular rejection or accelerated transplant atherosclerosis.

Another novel pharmaceutical agent with properties which may be of great interest in the treatment of transplant atherosclerosis or chronic graft rejection is *carvedilol*. Carvedilol is an anti-hypertensive pharmaceutical agent based on β -receptor and α -adrenoreceptor blockade (Ruffolo et al. 1992). Carvedilol also acts as an antioxidant through inhibition of the LDL cholesterol oxidation, inhibition of superoxide release from human neutrophils and inhibition of plasma membrane lipid peroxidation (Tian Li Yue 1992a, b, c, d). Furthermore, carvedilol has been shown to inhibit vascular smooth muscle cell proliferation *in vitro*. Irrespective of the stimulant of proliferation (endothelin-1, PDGF, EGF, thrombin or angiotensin-II) carvedilol efficiently inhibited the SMC proliferation (Cheng-Po Sung et al. 1993). Just recently it has also been shown to counteract PDGF-driven migration of smooth muscle cells. In experimental balloon angioplasty in the rat, several substances have been shown to reduce the degree of intimal hyperplasia by 35-70%. The reduction of the degree of intimal hyperplasia formation with carvedilol seems to be around 90%. In experimental myocardial infarction in the rabbit or in the pig, a substantial reduction in myocardial size was found following pretreatment with carvedilol (Feuerstein et al. 1992). In the experimental 5/6 nephrectomy model in the rat, leading to the development of glomerulosclerosis and proteinuria, these detrimental effects on the kidney may be reduced significantly through pretreatment with carvedilol. Thus, based on these experimental findings, carvedilol seems to have properties, that make it very promising for a future evaluation as an agent against the development of transplant atherosclerosis or chronic graft rejection.

SUMMARY AND CONCLUSION

Chronic rejection is a major threat towards the long-term function and survival of transplanted hearts and kidneys. It is characterized by a proliferative remodelling of the graft vessels along with structural changes of the parenchyma and gradual deterioration of graft function. The pathogenesis is complex and multifactorial. Since grafts with chronic rejection are also subjected to a more or less intense invasion of immunoreactive cells, an important primary objective is to optimize the immunosuppressive treatment. There is no established means of prevention or treatment of chronic rejection. Pharmacological agents interfering with prostaglandin metabolism have been tried most frequently and preliminary results are also available from the use of polyunsaturated fatty acids of the omega-3 series and of heparin derivatives. Based on experimental studies the somatostatin analogue angiopeptin seems very promising today. There will certainly be an increased interest in the use of lipid-reducing agents in the future as well as antioxidant agents acting against the effects of reactive oxygen radicals and oxidative modification of LDL fractions. A strong novel candidate is carvedilol, exerting both antihypertensive, antioxidant and antiproliferative properties.

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